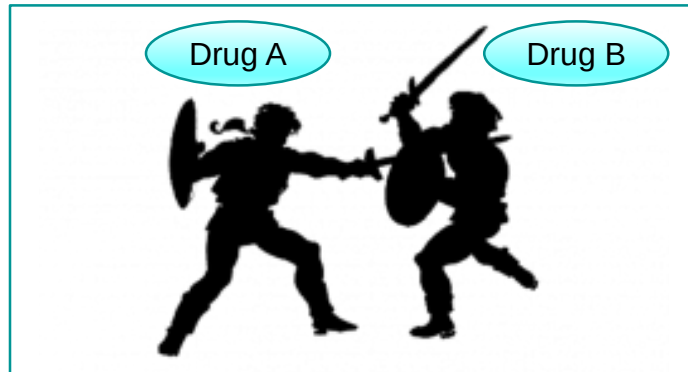




Drug Interactions

Dr. Tareq Al-Maqtari د طارق المقطري

PhD in Pharmacology from Univ of Louisville, USA

Who Am I?





Outline (not in order)

- 1) Types of interactions
- 2) Consequences
- 3) Mechanisms
- 4) Examples
- 5) Identification & prevention

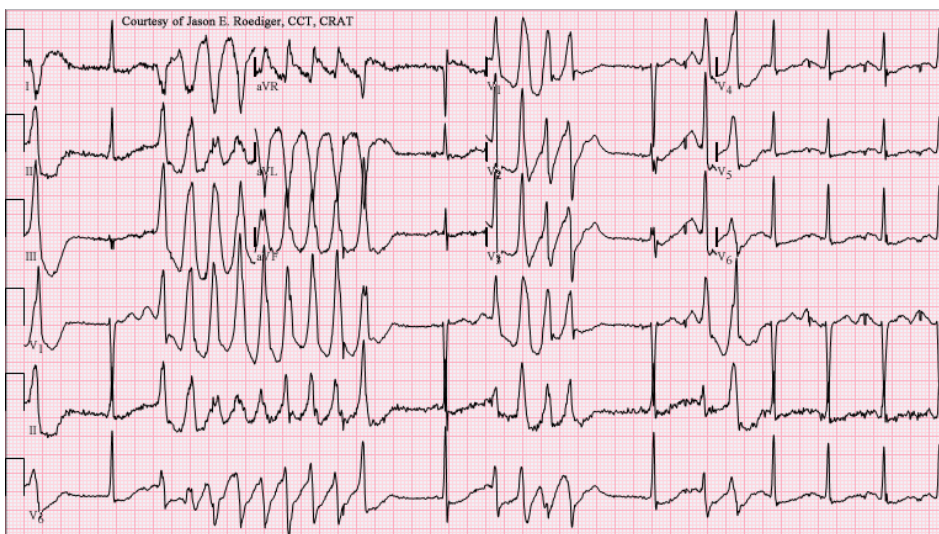
Drug Interactions

- * Drug-Drug Interactions
- * Drug-Food Interactions
- * Drug-Herb Interactions

First Drug-Drug Interactions

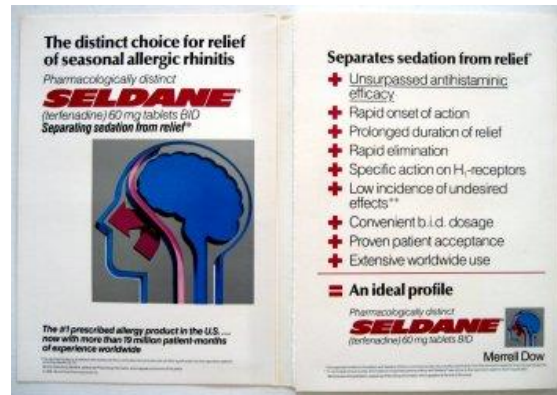


Case 1 (Torsades de pointes; in 1997)



What happened in 1997-1998?

- A 39-year-old woman on Terfenadine.



- Had Torsades de pointes = ventricular tachycardia
- Withdrawn from market (after 13 yrs of use!)

Details of Case 1

- 1- Terfenadine oral (60 mg x 2)
- 2- Cefaclor oral (250 mg x 3)
- 3- On day 8: ketoconazole oral (for vag. candida)



Complaint:

On day 8 → palpitation, intermittent syncope

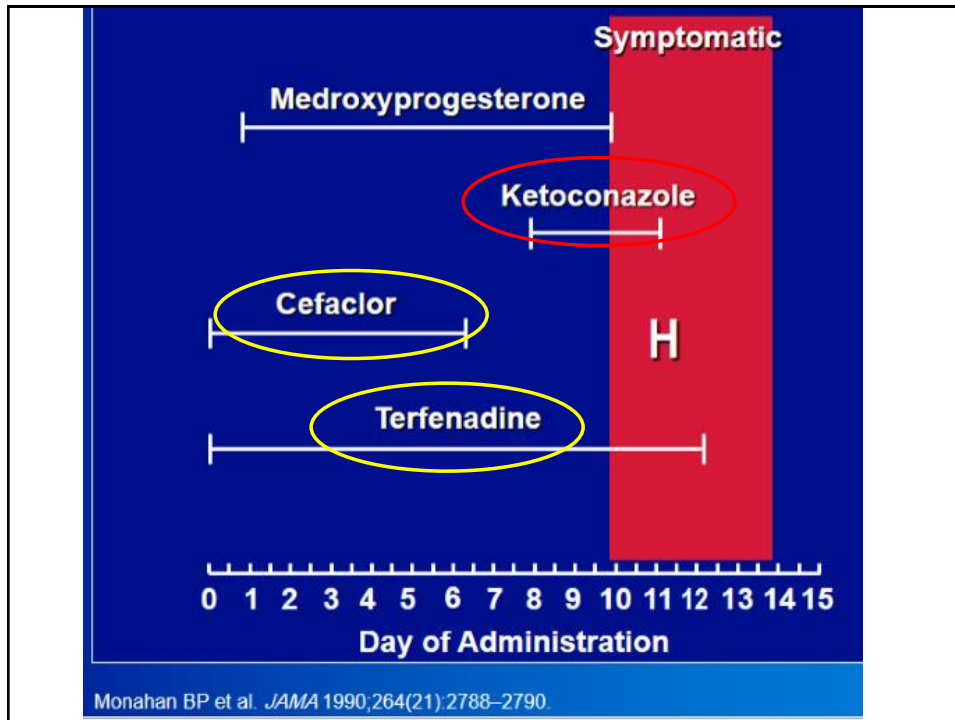
On day 10 → hospital admission.

Diagnosis:

Torsades de pointes (caused by terfenadine)

What happened next?

☺ Recovery after drug discontinuation.



End of a Drug “terfenadine; Seldane®”

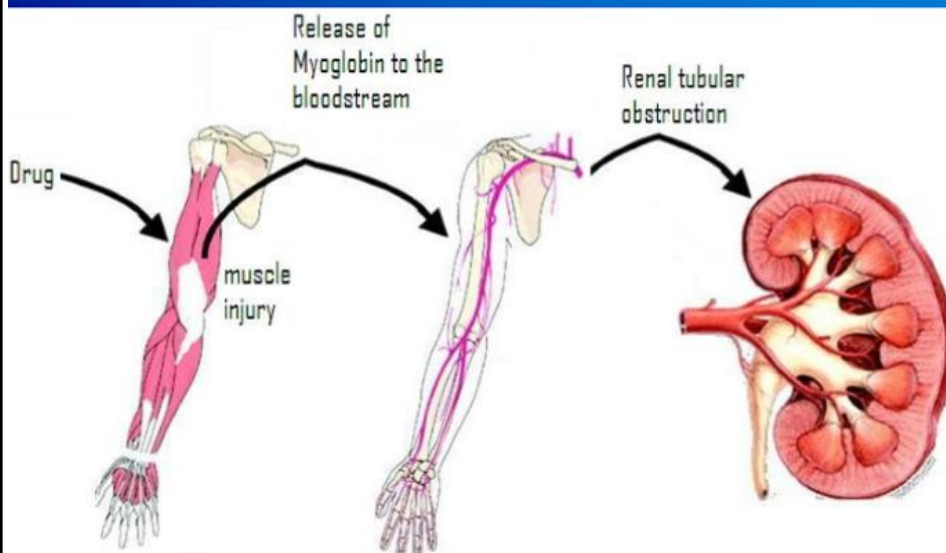
- Manufactured by Hoechst (“Sanofi” now)
- Entered the US in 1985
- The 1st non-sedating anti-H 🍌
- Led to arrhythmias (with CYP3A4 inhibitors)
- Withdrawn in 1998 🙄

What is ironic about it?

- Terfenadine is a prodrug of fexofenadine
- Fexofenadine was then introduced
- Fexofenadine is not toxic → still used!



Case 2: Rhabdomyolysis



Adapted from: Sinoway L, Li J. *J Appl Physiol* 2005;99:5–22.

Details of Case 2

76-yr pt. with atrial fibrillation

- Fluconazole (Diflucan®)
- Atorvastatin (Lipitor®)

Result:

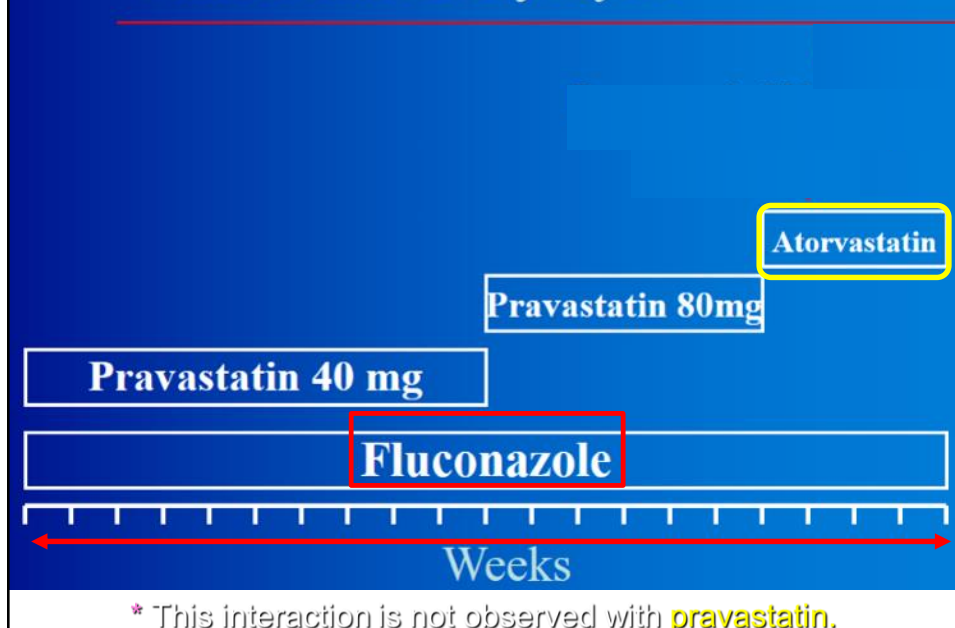
Rhabdomyolysis → renal failure → death

Explanation:

Fluconazole = ↓↓ CYP3A4

→ ↓ metabolism of atorvastatin

Fatal Rhabdomyolysis



Was atorvastatin withdrawn?

- No 😊

Blockbuster Drugs

Drug	Trade name	Company	Sales (billion \$) year
Atorvastatin	Lipitor	Pfizer	12.5 (2009)
Clopidogrel	Plavix	Bristol-Myers Squibb and Sanofi-Aventis	9.5 (2009)
Fluticasone and salmeterol	Advair	Glaxo-Smith-Kline	7.7(2009)
Enbrel	Etanercept	Amgen	6.2 (2009)
Valsartan	Diovan	Novartis	6.0 (2009)
Infliximab	Remicade	Johnson & Johnson	5.9 (2009)
Bevacizumab	Avastin	Roche and Genentech	5.7 (2009)
Rituximab	Rituxan	Roche and Genentech	5.6 (2009)
Adalimumab	Humira	Abbott	5.5 (2009))
Quetiapine	Seroquel	AstraZeneca	5.1 (2009)

Numbers about Drugs' Adverse Effects?

Drugs cause:

- serious SEs in 6.7% of hospitalized patients
- deaths in 44000-98000 pts / yr
- 177 billion \$ loss (morbidity & mortality)

Drug-drug interactions result in:

- 7000 deaths / yr



Some
withdrawn
drugs!

- Terfenadine (Seldane®) in 2/1998
- Bromphenac (Duract®) in 6/1998
- Astimezole (Hismanal®) in 6/1999
- Grepafloxacin (Raxar®) in 11/1999
- Troglitazone (Resulin®) in 3/2000
- Cisapride (Propulsid®) in 3/2000
- Rabcuronium (Raplon®) in 3/2001
- Cerivastatin (Baycol®) in 8/2001
- Dolsetron IV (Anzemet®) in 2010
- Propoxyphene (Darvon®) in 2011

Why do we have all these
drug problems?

New drugs tested only on ~ 3000 pts before marketing

Some drugs cause very rare toxicities

Some toxicities are caused by drug-drug interactions

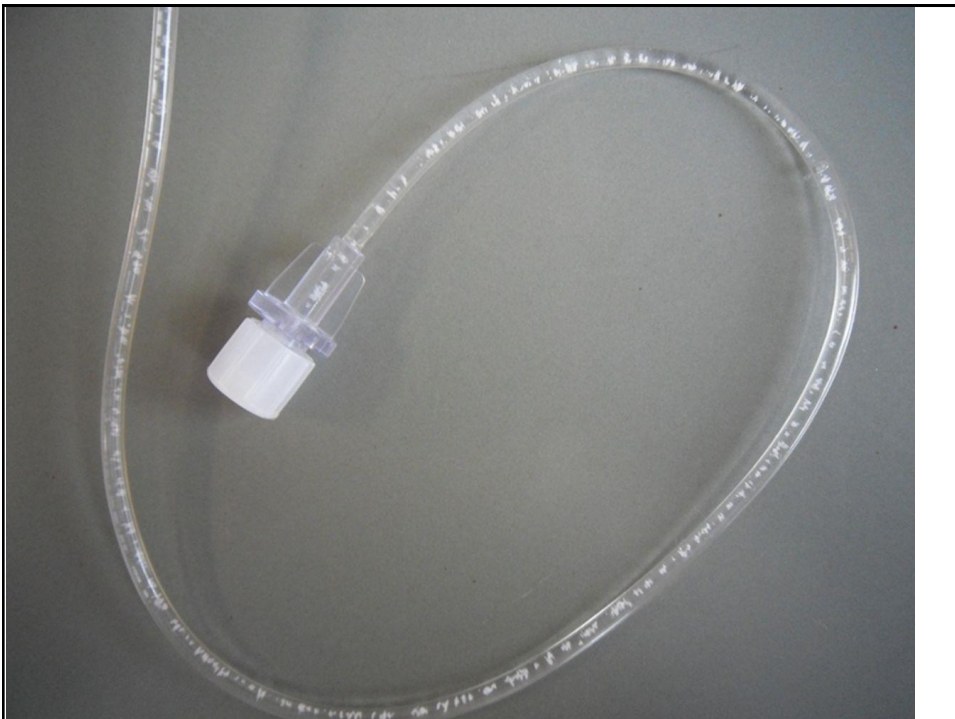
Remember!

Most drug-drug
interactions are
preventable!

Types of drug-drug interactions

1) Before administration

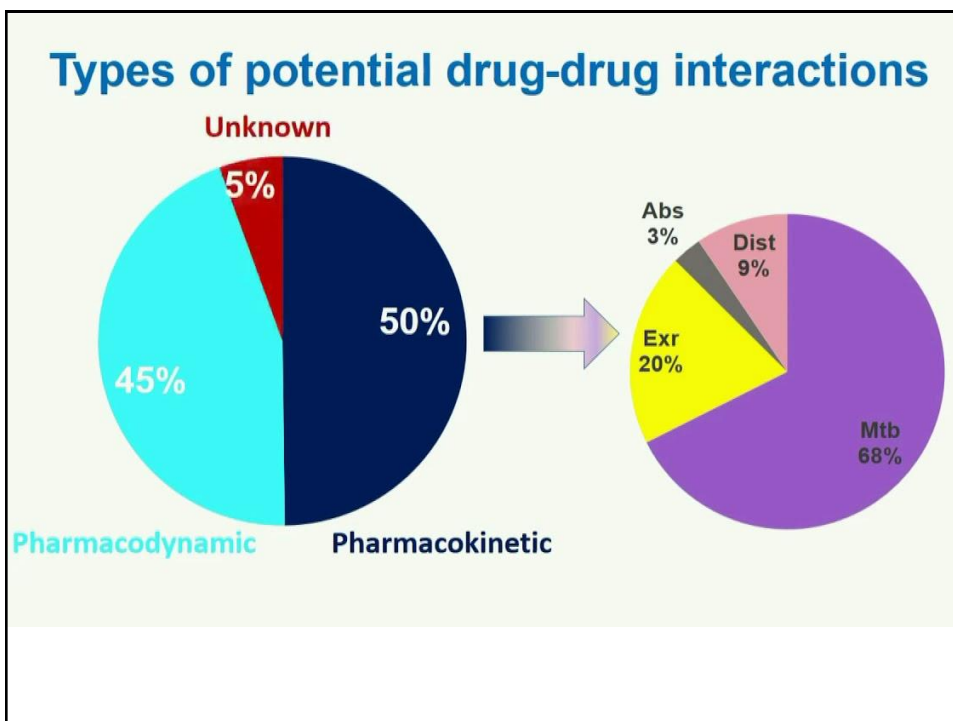
- Amphotericin B + normal saline
→ precipitation
- Phenytoin + 5% dextrose
→ precipitation
- Ceftriaxone + ringer lactate
→ precipitation
- Gentamicin + penicillins (in the same syringe)
→ inactivation



2) After administration

A) Pharmaco-kinetic Interactions

B) Pharmaco-dynamic Interactions



2) After administration

A) Pharmaco-kinetic Interactions

- Absorption:

Vit C + Fe or Ca

- Distribution:

Sulfonamides + oral hypoglycemics

- Metabolism**:

Phenobarbitone + oral contraceptives

- Excretion:

Probenicid + penicillin G

Interactions at:

→ absorption

At absorption

How can drug A affect absorption of Drug B?

1. $\uparrow\downarrow$ PH
2. $\uparrow\downarrow$ gastric emptying rate
3. $\uparrow$ complexes
4. $\downarrow$ transporters
5. $\uparrow$ mucosal damage

1. Altered PH

PPIs
H2 blockers

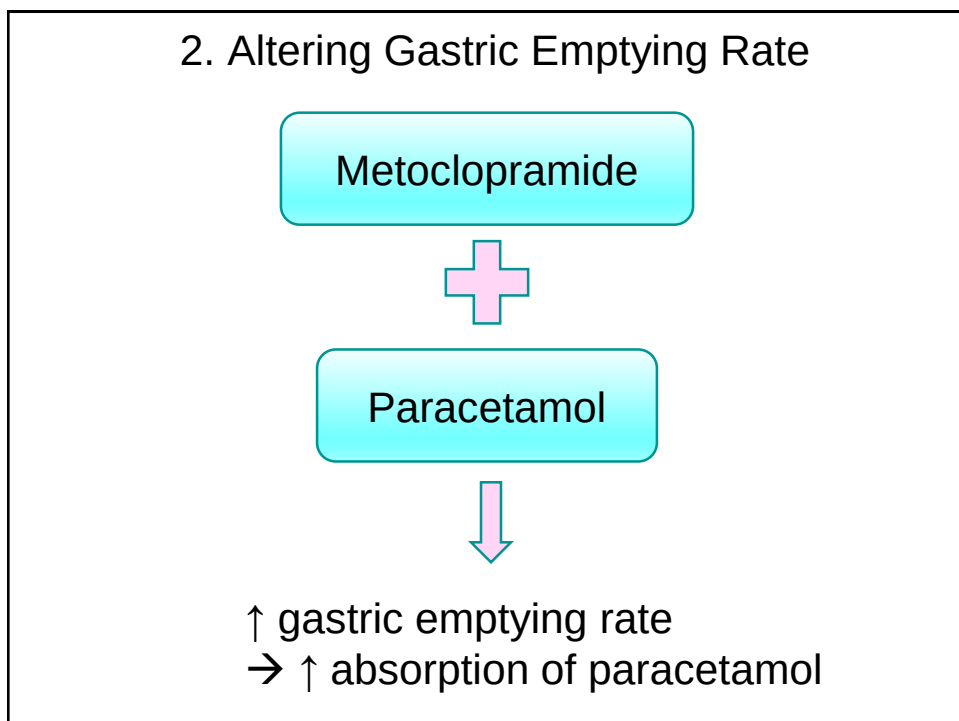
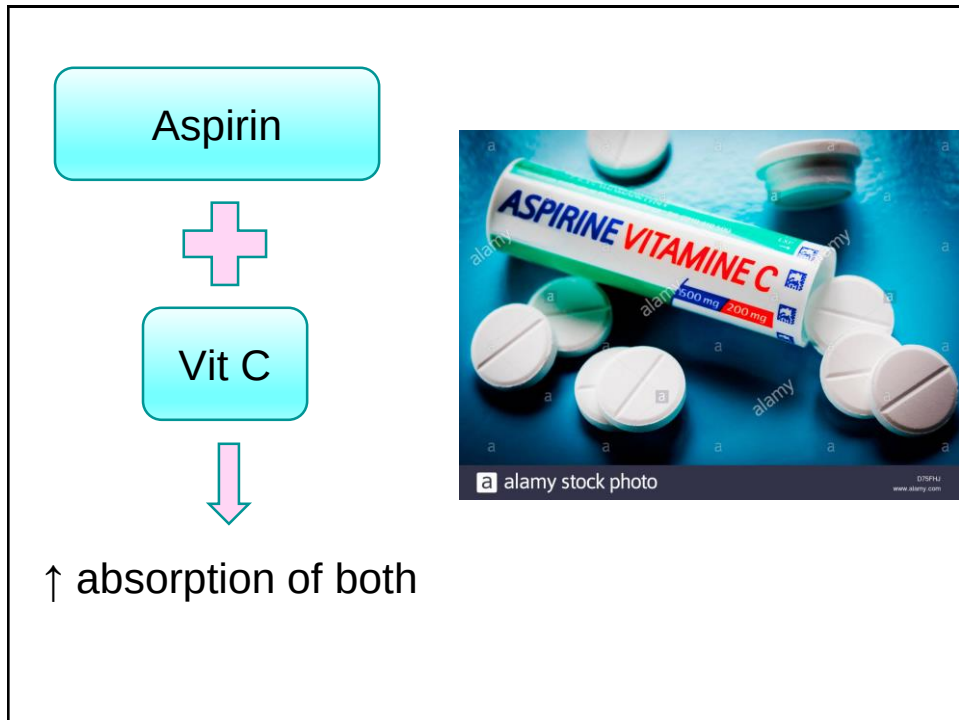


Ketoconazole



$\downarrow$ absorption of ketoconazole







3. Forming complexes

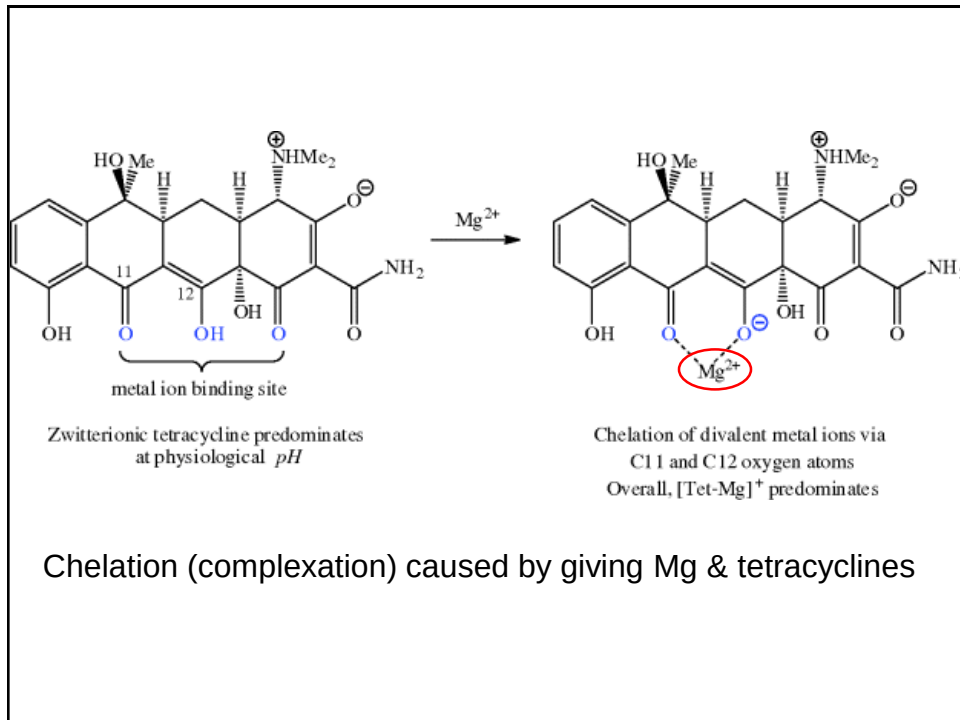
Tetracyclines, quinolones,
azithromycin



Calcium



↓ absorption (chelation)



4. Inhibiting a transporter

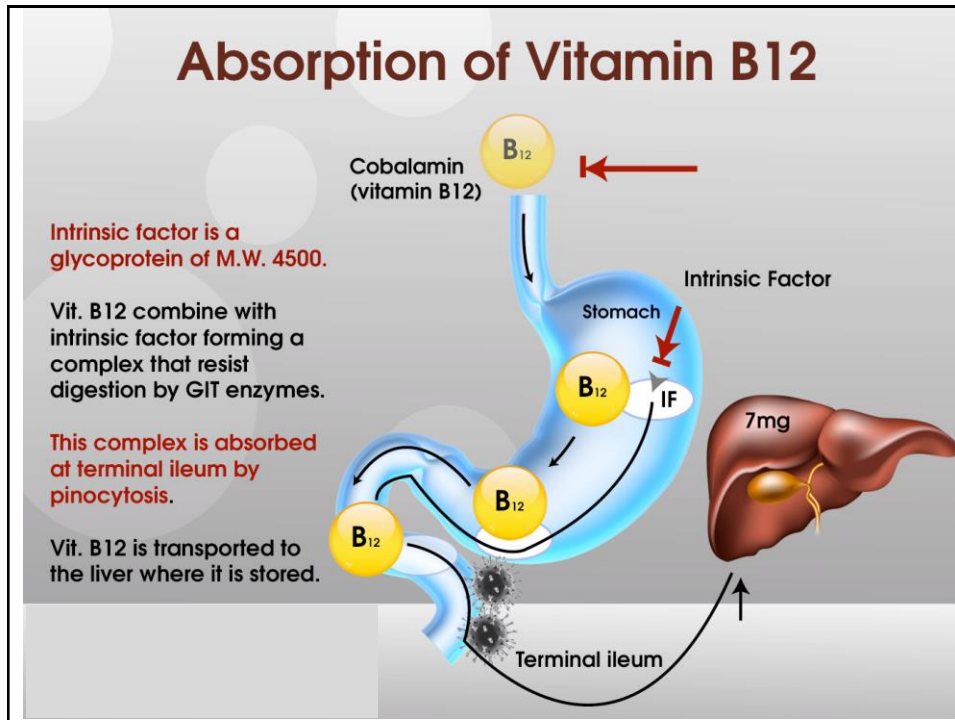
PPIs



Vit B12



↓ absorption of vit B12



5. Damaging the GIT mucosa

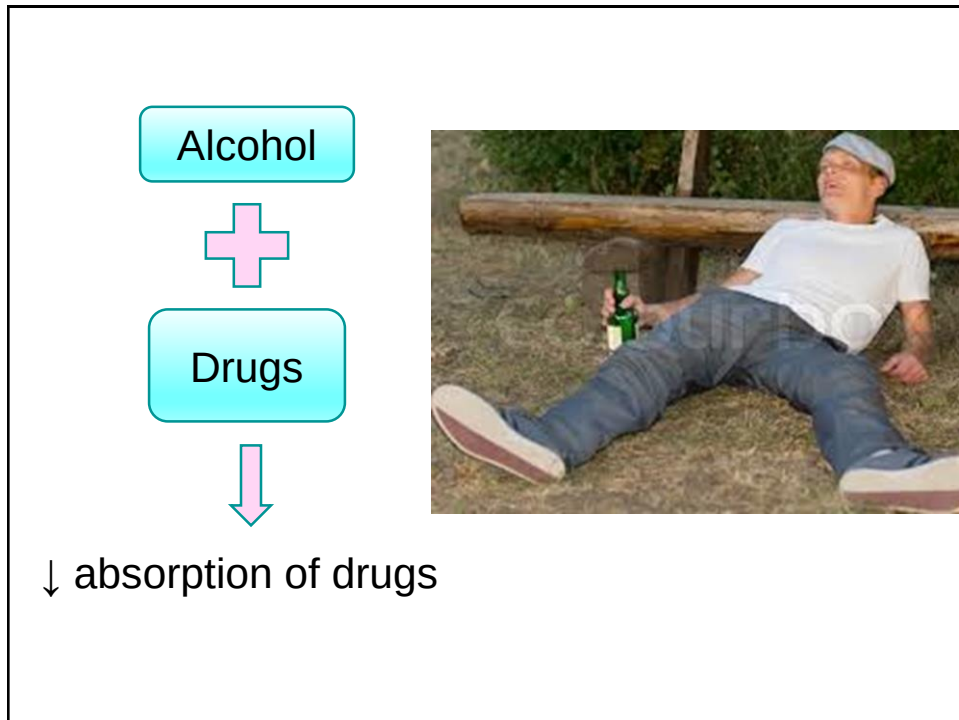
Anti-neoplastic drugs



Digoxin

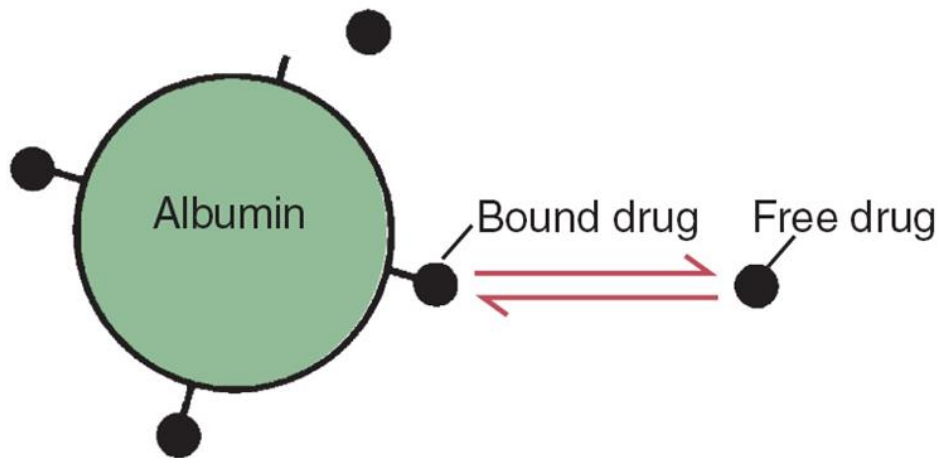


↓ absorption of digoxin



Interactions at:
- Distribution

Reversible Binding of a Drug to Albumin



(From Lehne RA: Pharmacology for nursing care, ed 7, St Louis, 2010, Saunders.)

Interactions at Distribution

- By displacement (bumping) interactions
- Occur when giving 2 drugs with strong plasma protein binding.
- Irrelevant mostly (clinically)!
 - The $\uparrow\uparrow$ in the free form, is $\downarrow\downarrow$ by elimination.
 - Most displacement interactions are due to $\downarrow$ elimination
- Drugs that are known to displace others are:
 - 1) Aspirin
 - 2) Sulfonamides
 - 3) Valproic acid

(Ex. 1) Distribution

Aspirin



Warfarin



↑ free form & toxicity of warfarin

(Ex. 2) Distribution

Sulfonamides



Tolbutamide



↑ free form & toxicity of
tolbutamide

(Ex. 3) Distribution

Valproic acid



carbamazepine



↑ free form of
carbamazepine

(Ex. 4) Distribution

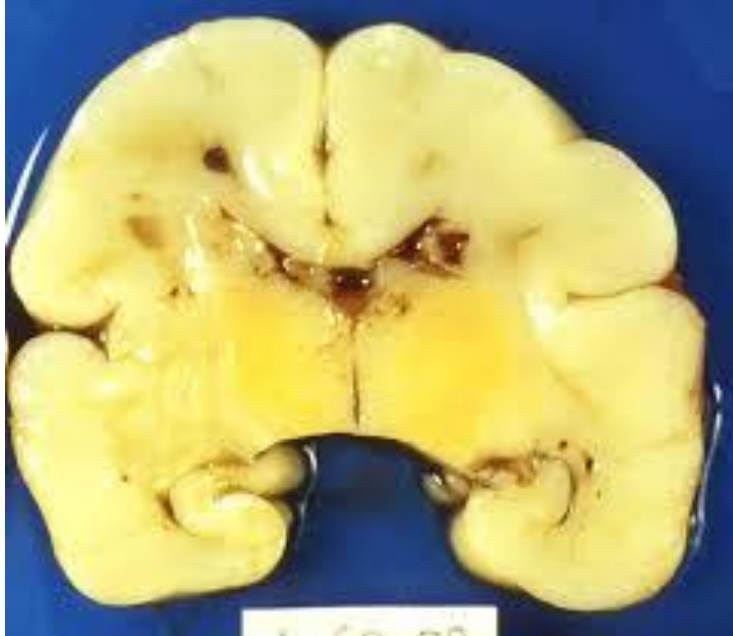
Sulfonamides



In neonates



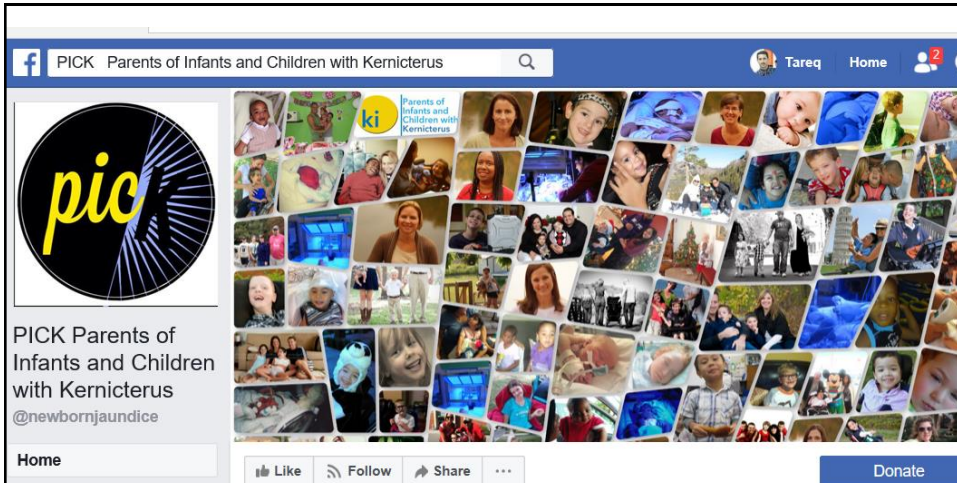
Kernicterus!
(no treatment so far)!



Kernicterus in the brain



Kernicterus may lead to cerebral palsy



The image shows a screenshot of a Facebook page for 'PICK Parents of Infants and Children with Kernicterus'. The page features a circular logo with the word 'pick' in yellow and black. The cover photo is a large collage of many small photos of parents and children. The page has a search bar at the top, a navigation bar with 'Tareq', 'Home', and a notification icon, and a 'Donate' button. The main content area shows a grid of photos of parents and children. Below the photos, there are buttons for 'Like', 'Follow', 'Share', and a menu icon.

PICK Parents of Infants and Children with Kernicterus
@newbornjaundice

Home

Like Follow Share ... Donate

Pick = Parents of Infants & Children with Kernicterus

Interactions at:
→ Metabolism

Metabolism Interactions

- ❶ Microsomal enzyme inducers (**2-3 wks for induction**)
→ ↑ metabolism of other drugs
- ❷ Microsomal enzyme inhibitors (**fast; within 24 h**)
→ ↓ metabolism of other drugs

Phases of Metabolism

❶ Phase I:

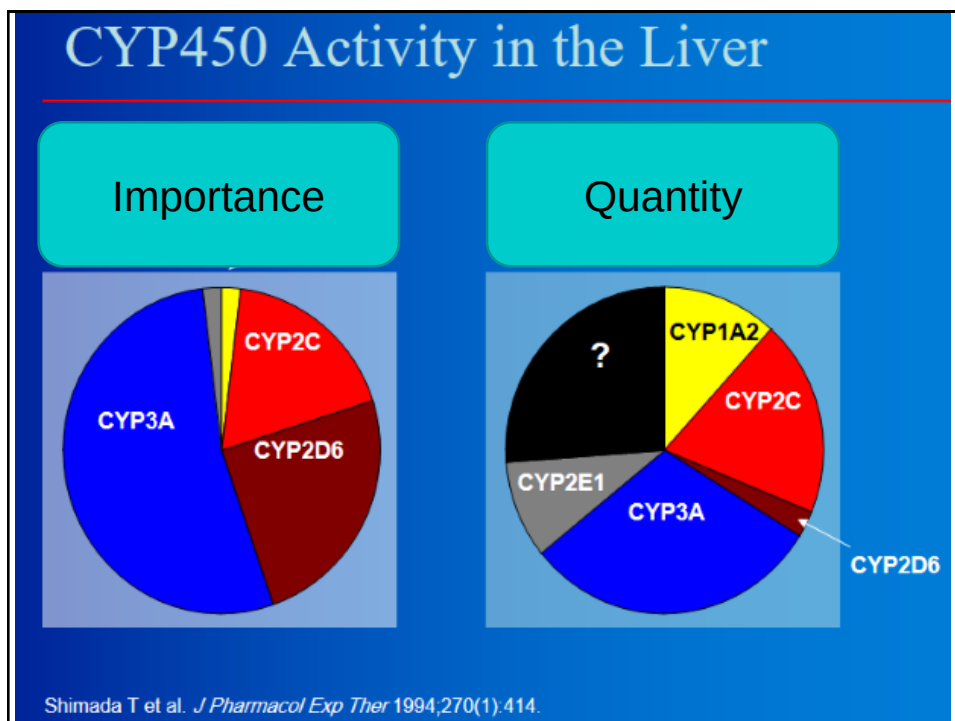
- Done mainly by CYP450
- include:
 - oxidation*
 - reduction
 - hydrolysis

❷ Phase II (conjugation)

- Adds a big H₂O-soluble entity
(glucoronate*, acetate, glutathione, methyl, glycine...)

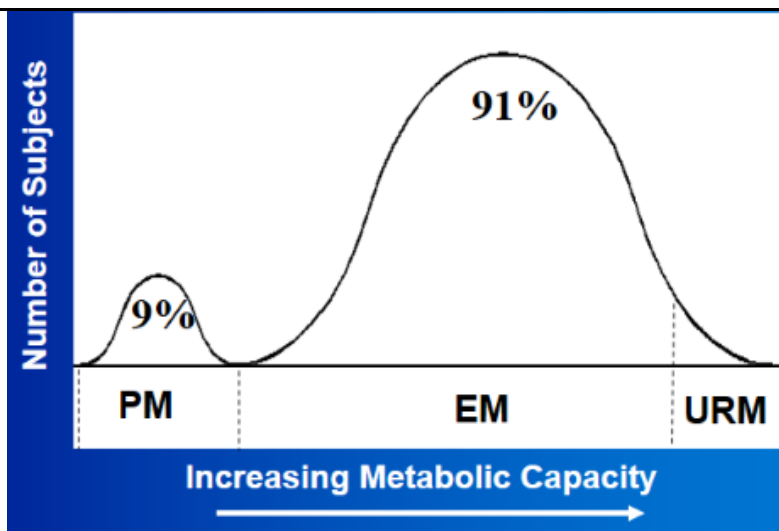
Cytochrome P450

- Does most phase I metabolism
- Usually oxidize drugs (forming -OH)
- Major enzymes:
 - 1A1, 1A2
 - 2C9, 2C19, 2D6, 2E1
 - 3A4 *



Remember

- 1) Quantity is not related to the role
 - e.g. CYP2D6
- 2) A huge variability exist
 - e.g. CYP2D6



Population drug metabolism distribution for CYP2D6

PM = Poor Metabolizers;

EM = Extensive Metabolizers;

URM = Ultra-Rapid Metabolizers (multiple gene copies!)

(Ex. 1) Metabolism Interactions

Phenytoin



Oral contraceptives



↓ activity of oral contraceptives



(Ex. 2) Metabolism

Omeprazol

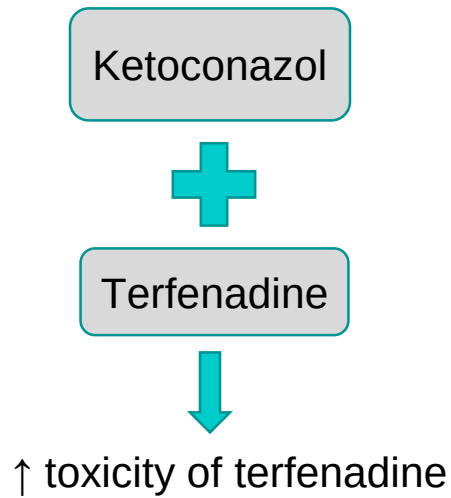


Clopidogrel

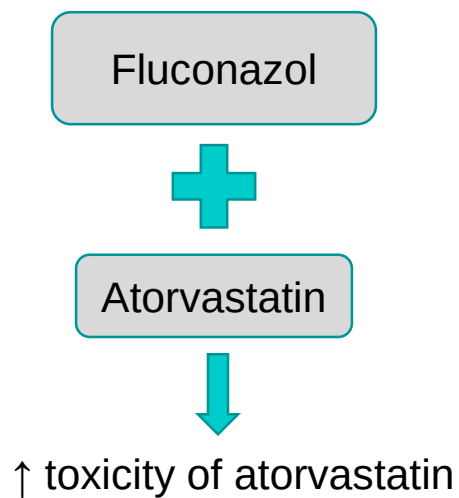


↓ activity of clopidogrel

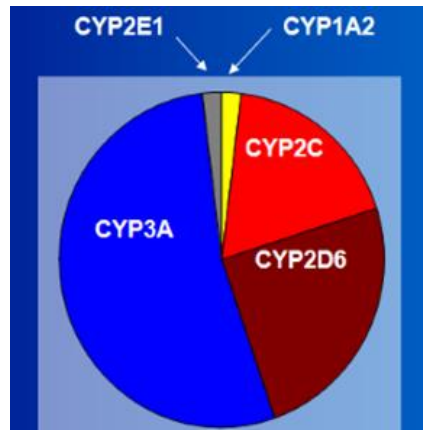
(Ex. 3) Metabolism



(Ex. 4) Metabolism



More details about individual CYP450 enzymes



1) CYP 3A4

- The most important drug metabolizer
- Metabolizes most of the following drugs:
 - 1) CCBs
 - 2) statins
 - 3) 2nd generation anti-H
 - 4) BZs
 - 5) cyclosporine
 - 6) HIV protease inhibitors

- The basis for most fatal interactions
(involved in the 2 cases described previously)
- Its inhibition led to withdrawal of several drugs:
 - Terfenadine
 - Astemizole
 - Cisapride
 - Mibefradil (CCB)
 - Levomethadyl (treats opioid dependence)

Q- Which drugs $\uparrow\uparrow$ CYP 3A4?

→ Antiepileptics
(carbamazepine, phenytoin, phenobarbitone)

Q- Which drugs $\downarrow\downarrow$ CYP 3A4?

→ Antibiotics & antifungals
(erythromycin, clarithromycin, chloramphenicol, ciprofloxacin)
(ketoconazol, fluconazole, itraconazol)

→ Grapefruit



Which is faster:
CYP induction or inhibition?

- CYP inducers take 2-3 weeks for max induction
- CYP inhibitors take hrs for inhibition

Which is more serious:
CYP induction or inhibition?

- CYP induction usually leads to ↓↓ efficacy of drugs
- CYP inhibition usually leads to ↑↑ toxicity of drugs

Spot the potential interaction?

- 1- Verapamil + Clarithromycin
- 2- Atorvastatin + Phenobarbitone
- 3- Diltiazem + Carbamazepine
- 4- Atorvastatin + Grape fruit juice

2) CYP2D6

(metabolize many CVS & psychotropics drugs)

- Metabolize: - most β blockers
 - many TCAs
- Inhibited by: - Quinidine
 - Fluoxetine, paroxetine & haloperidol

Application 1

1) A psychiatrist prescribed the following:

- paroxetine
- Tricyclic antidepressant

What do you think?

Application 2

2) A chest doctor prescribed the following:

- Quinidine
- β blocker?

What is the problem?

3) CYP2C9

- Metabolize: - Most NSAIDs (antiinflammatory)
 - Warfarin (anticoagulant)
 - Phenytoin (antiepileptic)
- Inhibited by: - fluconazole (antifungal)
 - metronidazole (antiaprotzoal)
 - co-trimoxazole (antibacterial)

* CYP2C9 metabolize even the COX-2 selective drugs

Application 1

A doctor prescribed fluconazole to treat a fungal infection in a patient using warfarin?

What is the problem?

Application 2

A doctor prescribed co-trimoxazole in a patient using phenytoin?

What is the problem?

* Phenytoin follows 0 order elimination at higher doses, so increased concentrations results in greater toxicity.

4) CYP2C19

- Absent in 20-30% of Asians
- Metabolize: - Diazepam
 - Clopidogrel
- Inhibited by: - Ketoconazole
 - Omeprazol

Application 1

1) A doctor prescribed omeprazole to treat peptic ulcer in a patient using clopidogrel (Plavix®)?

What is the problem?

Is there a solution?

Application 2

2) A doctor prescribed ketoconazol to treat peptic ulcer in a patient using diazepam?

What is the problem?

5) CYP1A2

- Metabolize: - Theophylline (& caffeine)
 - Imipramine (& amitriptyline)
- Inhibited by: - Ciprofloxacin
 - Cimetidine
- Induced by smoking

Application 1

1) You would like to prescribe Theophylline to a heavy smoker?

Q) What would you change in the prescription?

The dose of theophylline

Application 2

2) Ciprofloxacin for UTI in a patient using imipramine?

What do you think?

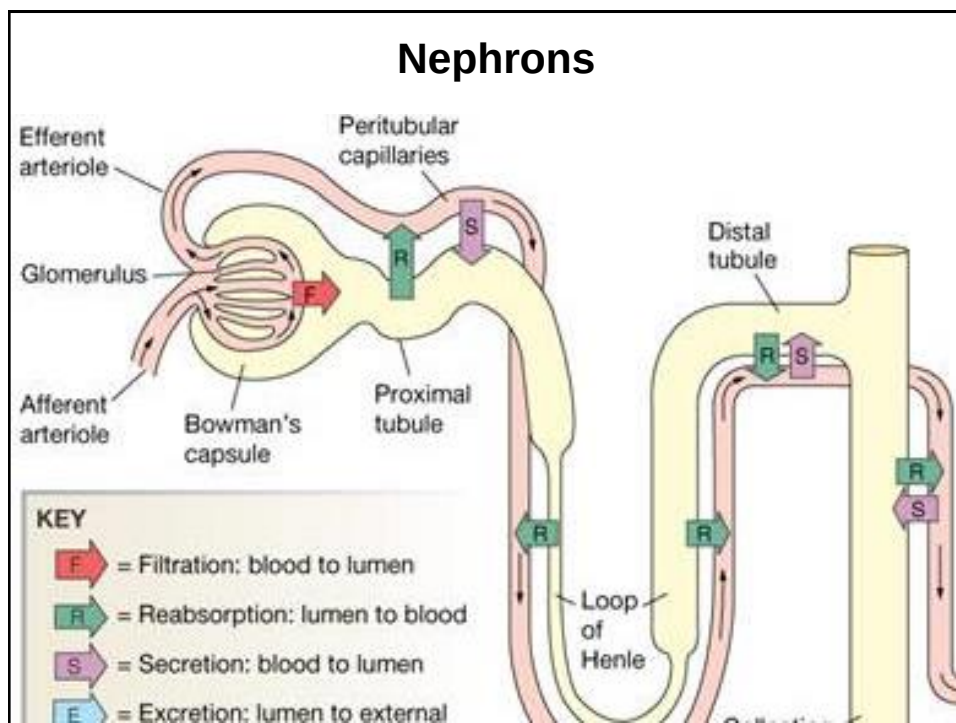


- Can 1 drug induce several enzymes?
- Can 1 drug inhibit several enzymes?

Interactions at
→ Excretion

- 1) In the kidney
- 2) Enterohepatic cycling

1) In the kidneys



Excretion is the net result of 3 processes

1. Glomerular filtration

2. Tubular reabsorption

2. Tubular secretion

Interactions in the kidneys

At “tubular re-absorption” or “active secretion”:

a) At tubular re-absorption:

- Acidification of urine.
 - ⇒ ↑ excretion of weak bases (e.g. amphetamine)
- Alkalinisation of urine.
 - ⇒ ↑ excretion of weak acids (e.g. barbiturates)

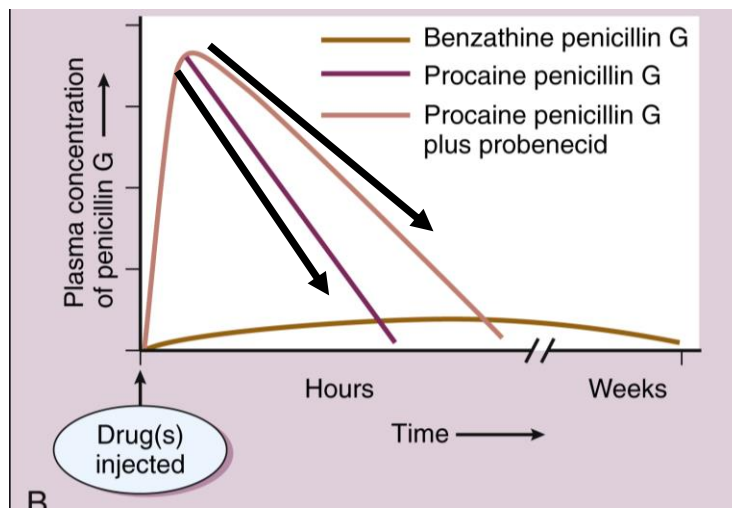
b) At active secretion (competition)

In the proximal tubule, several pumps exist:

- Pump for weak acids (e.g. penicillins)
- Pump for weak bases (e.g. morphine)
- P-glycoprotein (e.g. digoxin)
- others

Example 1

Probenicid + penicillin G $\Rightarrow$ $\uparrow$ effect 😊



Example 2

```
graph TD; A[Digoxin] -- "+" --> B[Quinidine]; B --> C["↓ excretion of Digoxin"]
```

Digoxin



Quinidine



↓ excretion of Digoxin

Example 3

```
graph TD; A[Digoxin] -- "+" --> B[Verapamil]; B --> C["↓ excretion of Digoxin"]
```

Digoxin



Verapamil



↓ excretion of Digoxin

Example 4

Loperamide

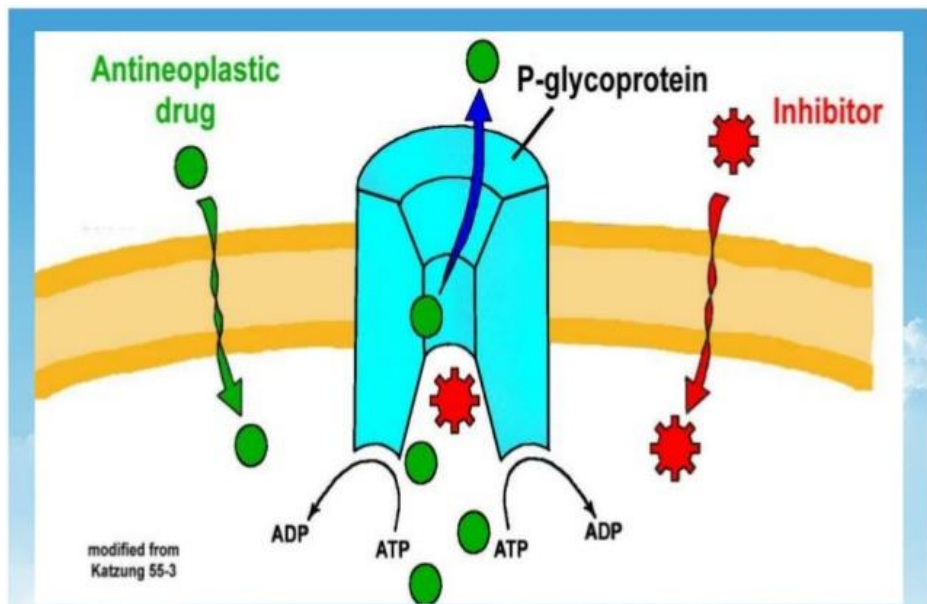


Quinidine



→ Addiction to loperamide

What are P-glycoproteins?

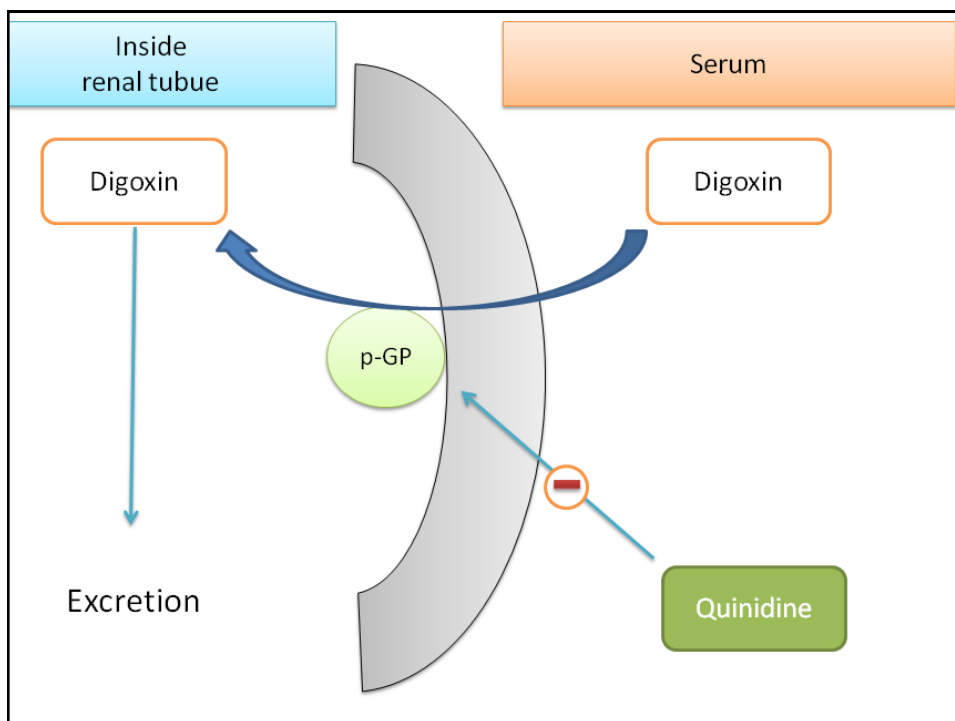


P-glycoprotein inhibitors

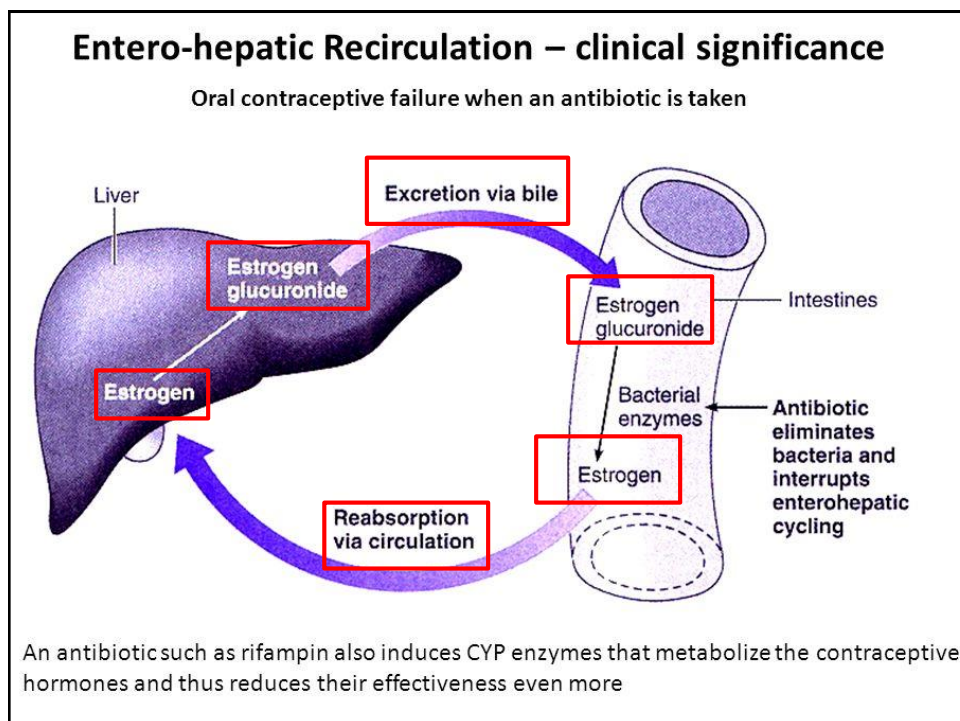
- Quinidine & verapamil
- Erythromycin & clarithromycin
(also inhibit CYP3A4)

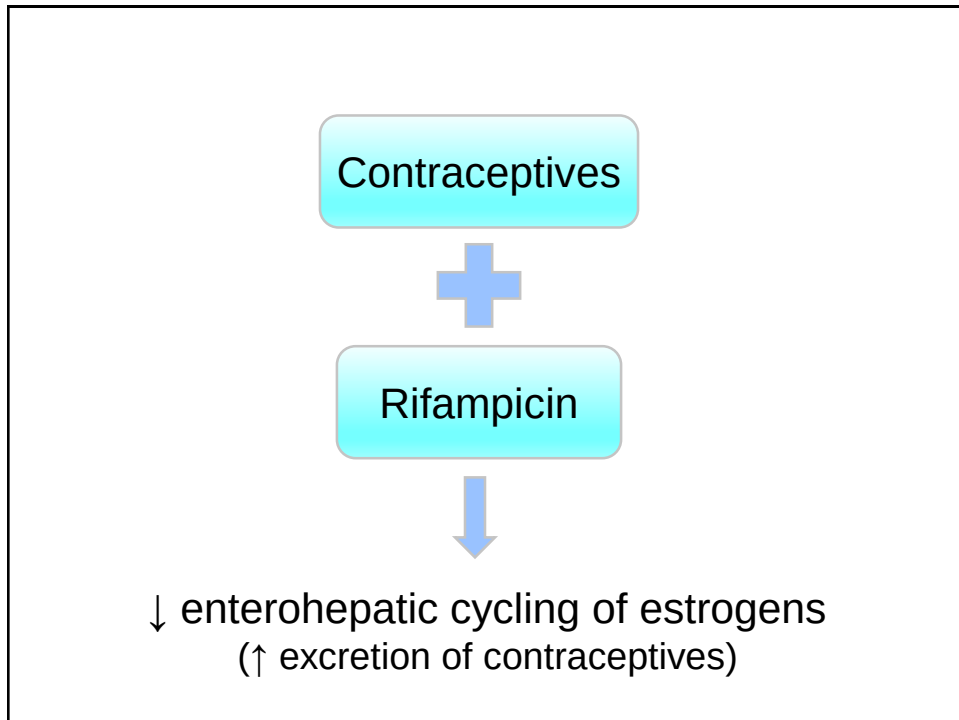
* Note that CYP3A & P-glycoproteins:

- act on similar drugs (CCBs & statins)
- inhibited by similar drugs (erythromycin & clarithromycin)



2) Enterohepatic cycling

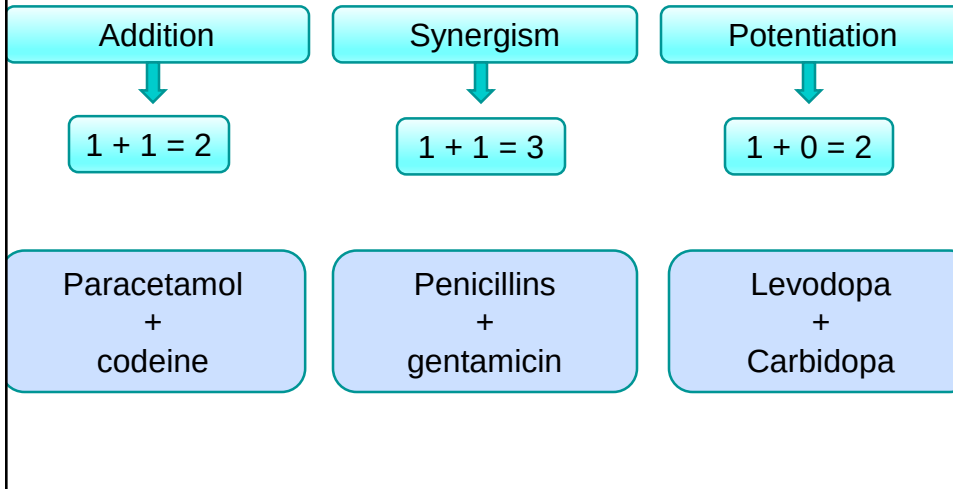


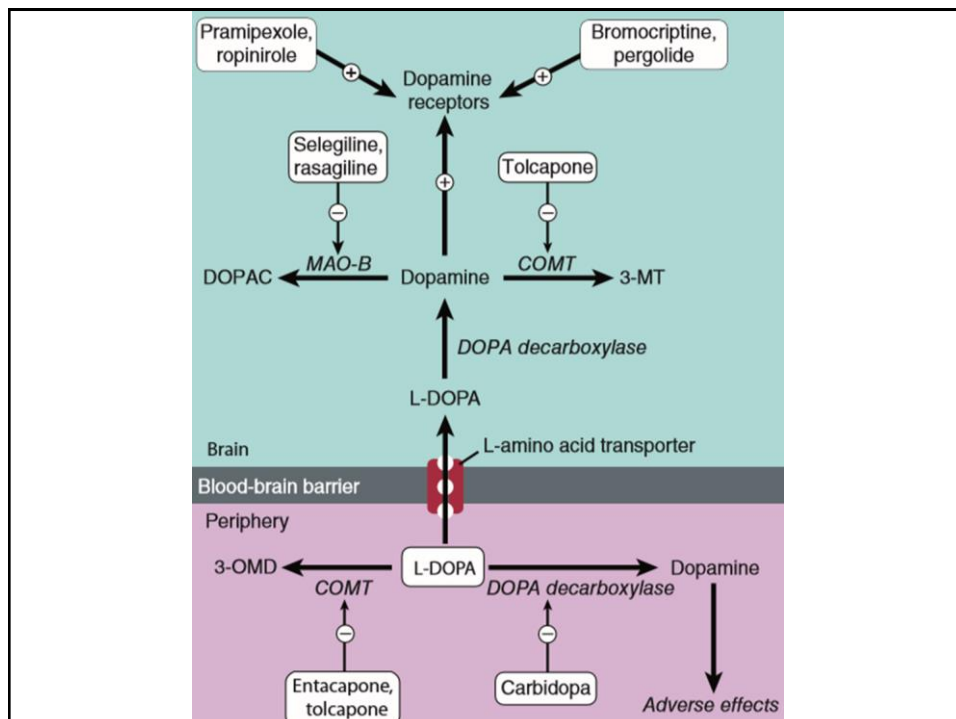
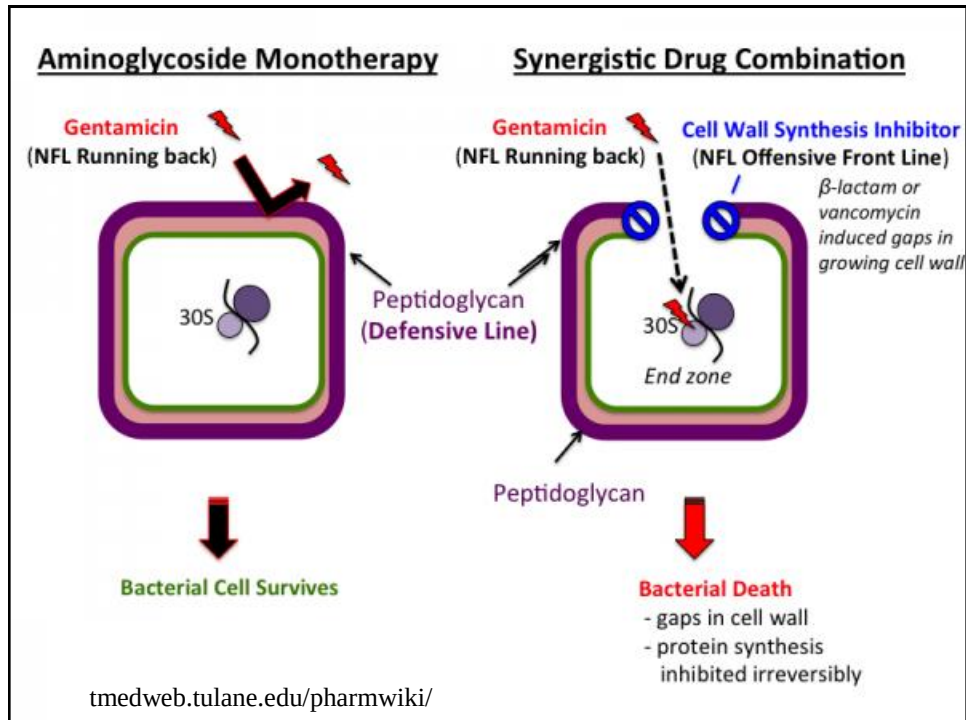


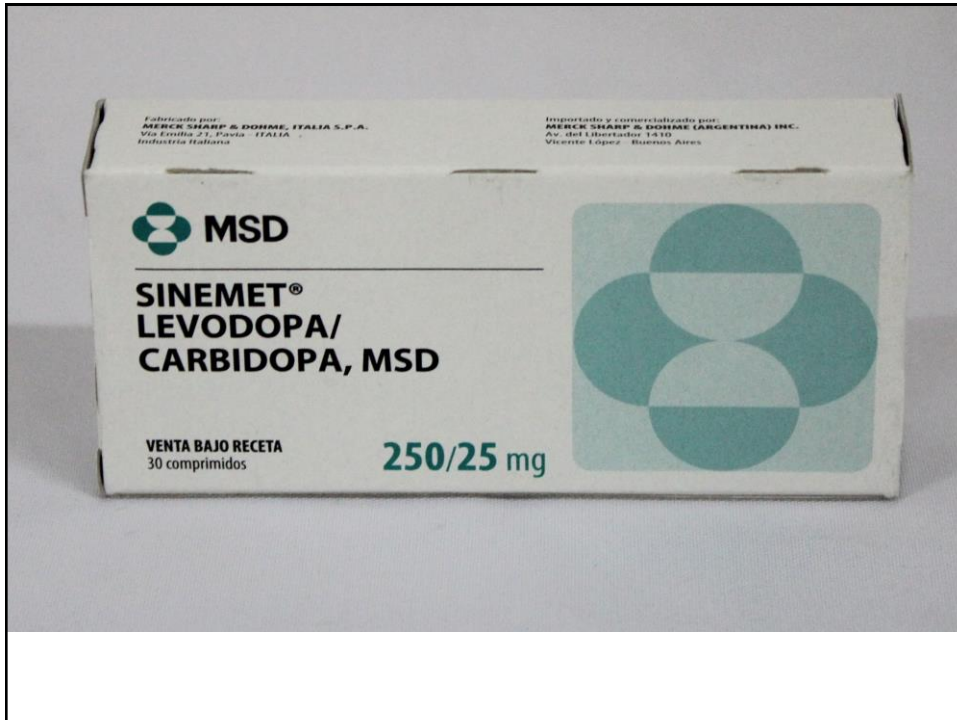
B) Pharmacodynamic interactions

B) Pharmaco-dynamic interactions

1) ↑↑↑ effect:







Is ↑↑↑ effect good or bad?

A) Can be good (↑ efficacy)
(like the previous examples)

B) Can also be bad (↑ toxicity)

Ex. 1

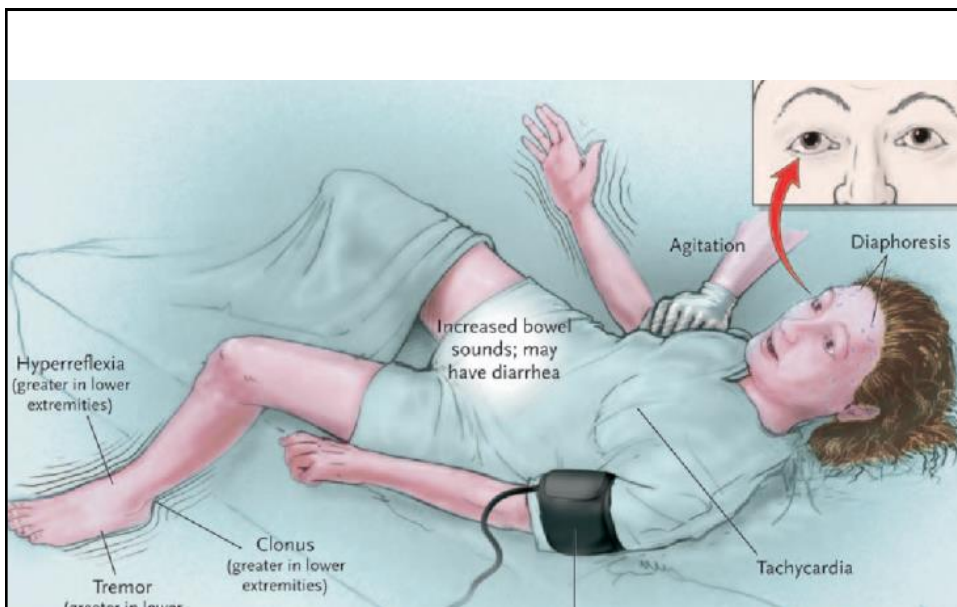
TCA_s



SSRIs



Serotonin syndrome!



Serotonin syndrome

Ex. 2

β
blocker



verapamil



Heart block or cardiac arrest!

Ex. 3

Metformin



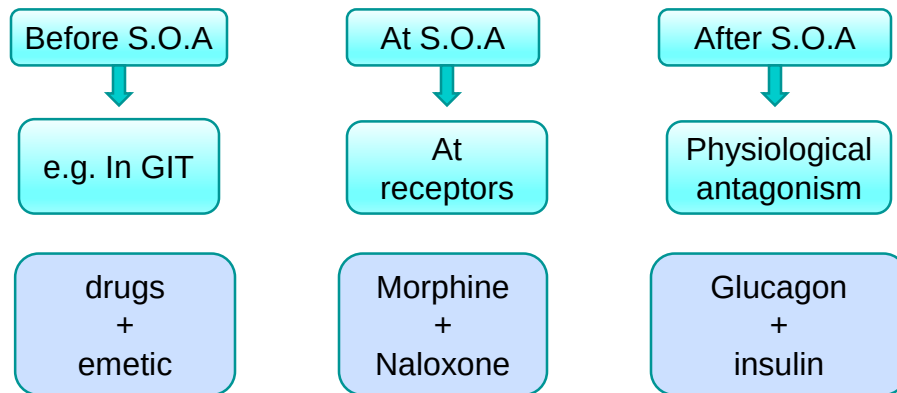
Glipizide



Hypoglycemia
(may also good in late stages of DM)

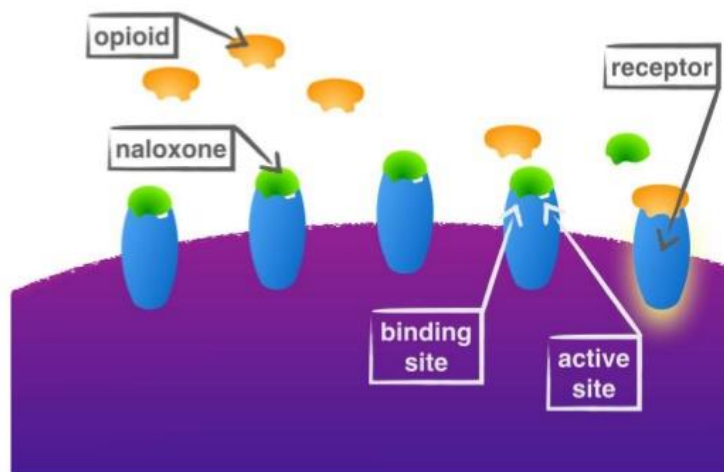
B) Pharmaco-dynamic interactions

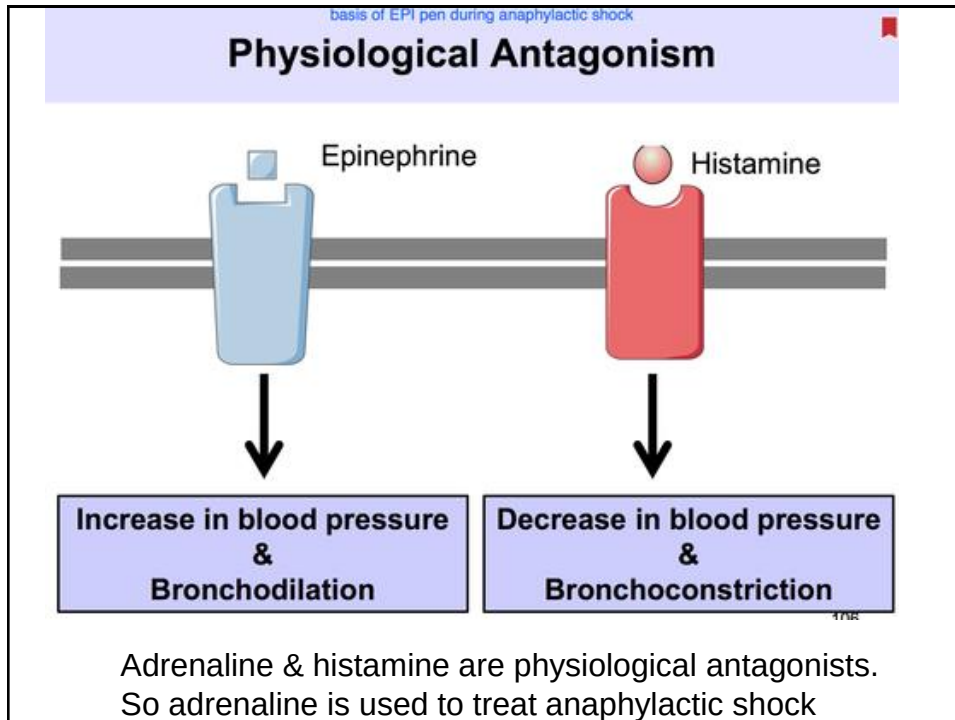
2) ↓↓↓ effect (antagonism):



S.O.A = site of action

Naloxone: mechanism of action





Antagonism

→ Can be good (↓ toxicity)

Example 1

Warfarin



Vit K



Tx warfarin toxicity

Example 2

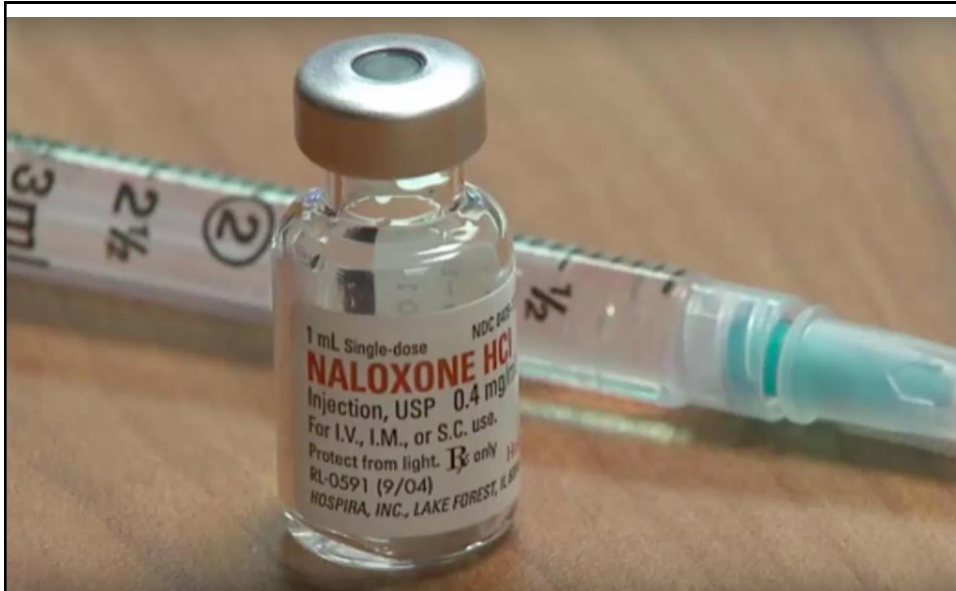
Morphine



Naloxone



Treats morphine Toxicity



Naloxone is used for treating
opioid toxicity

Antagonism

→ can also be bad (↓ efficacy)

Example 1

Oral hypoglycemics



Betamethasone



↓ effect of oral hypoglycemics

Example 2

Risperdone



L-dopa



↓ antipsychotic effect of risperidone

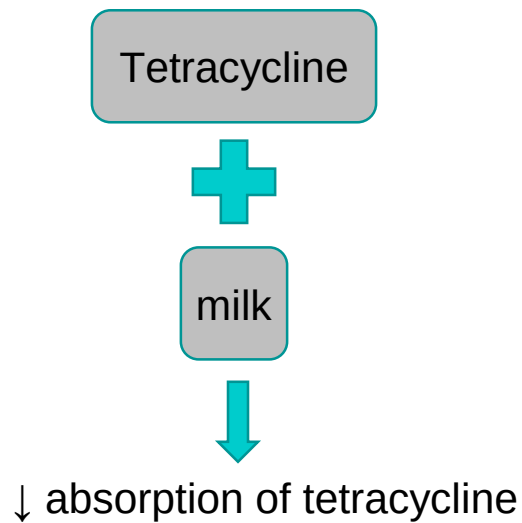
Second

Drug-Food Interactions

A- The food may affect drugs

B- The drug may affect food

1) with milk



2) With leafy vegetables

Warfarin



Spinach



↓ effect of warfarin

3) with grapefruit juice

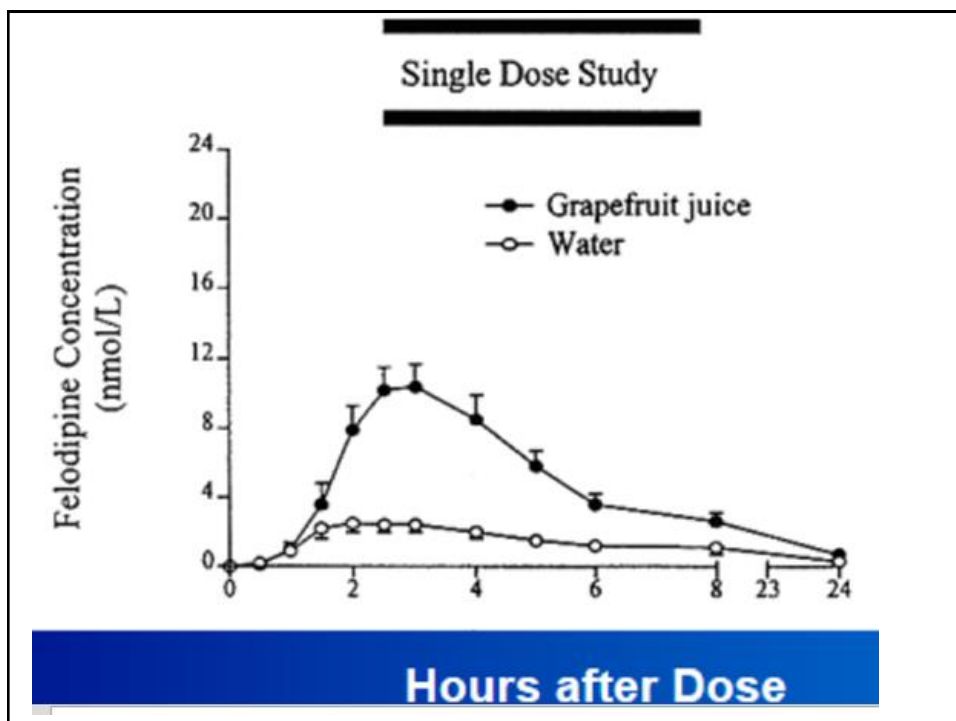
Grapefruit
Juice



felodipine



↓ metabolism of felodipine



4) With cheese

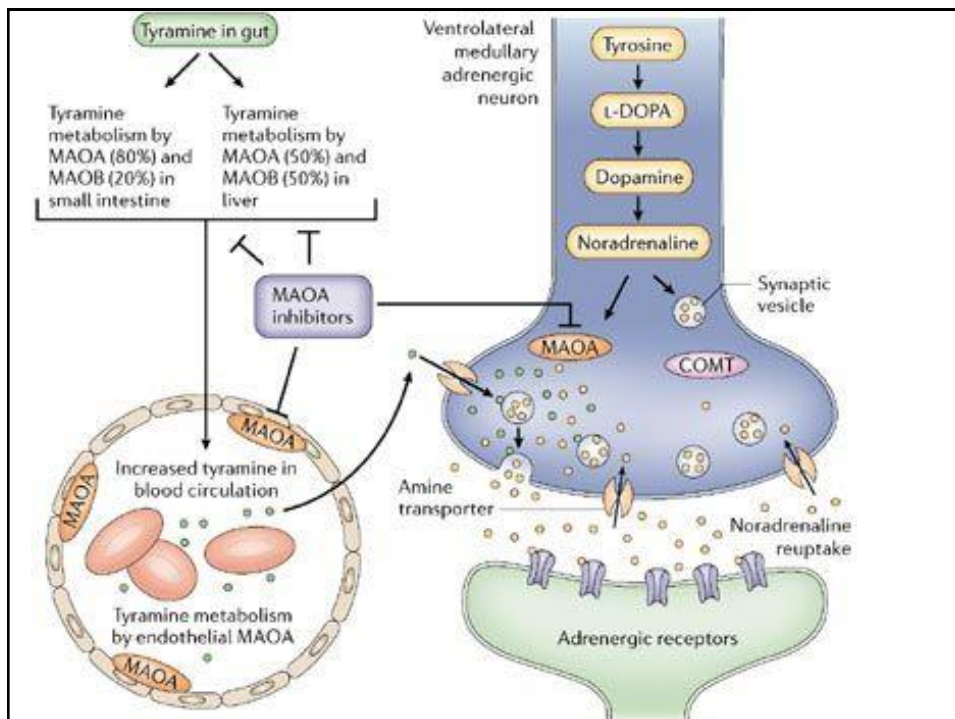
Phenylezsin

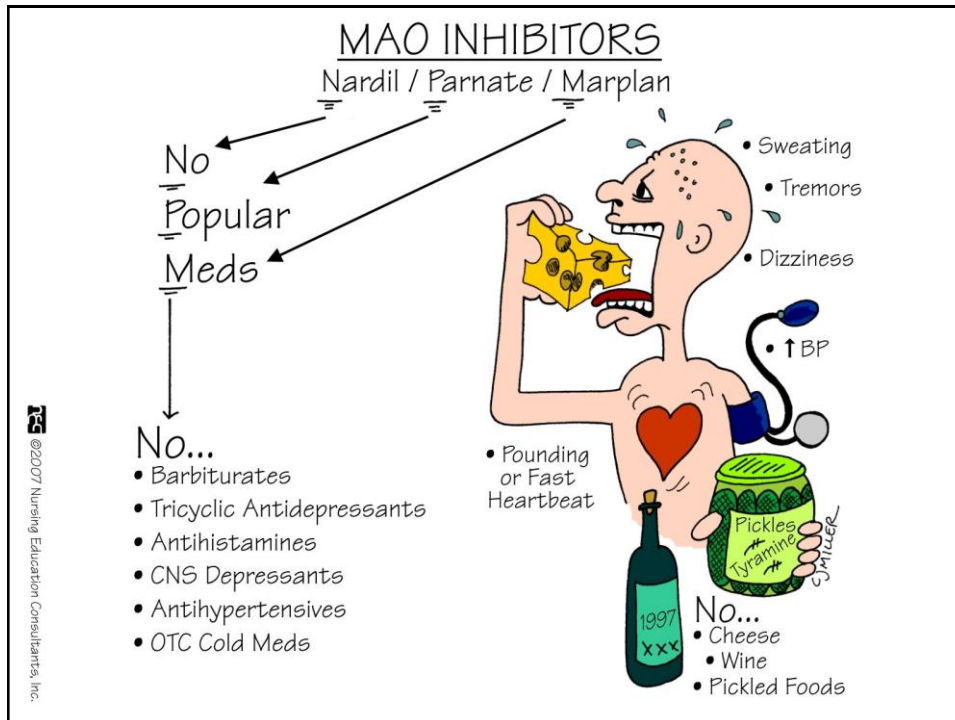


Cheese



Emergency hypertension





5) With alcohol

Diazepam



Alcohol



↓↓↓ CNS

6) With vitamins

Anti-Hyperlipidemic



Fat-soluble vitamins
(of food)



↓ absorption of vitamins

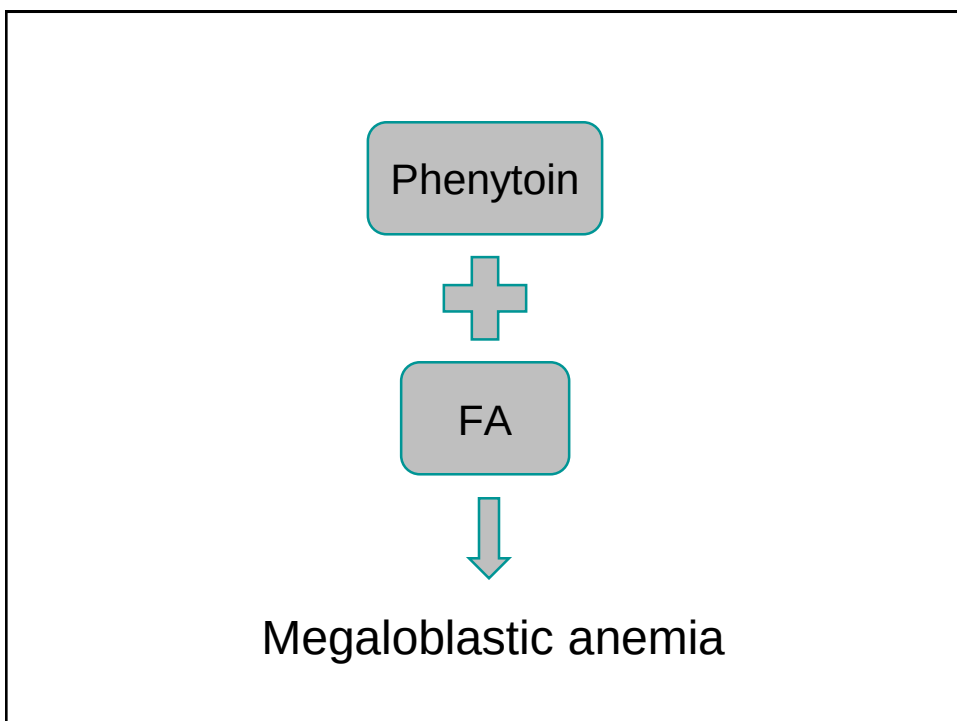
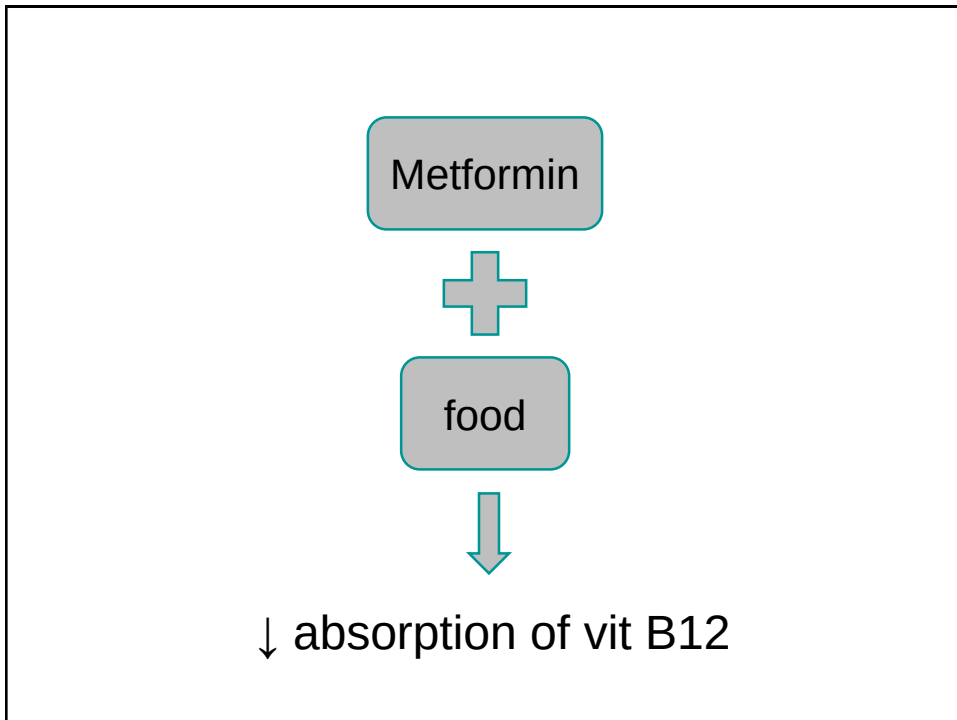
PPIs



food



↓ absorption of vit B12



Third

Drug-Herb Interactions

St John's wort

- Induces CYP 3A4
- Increase 5HT in CNS



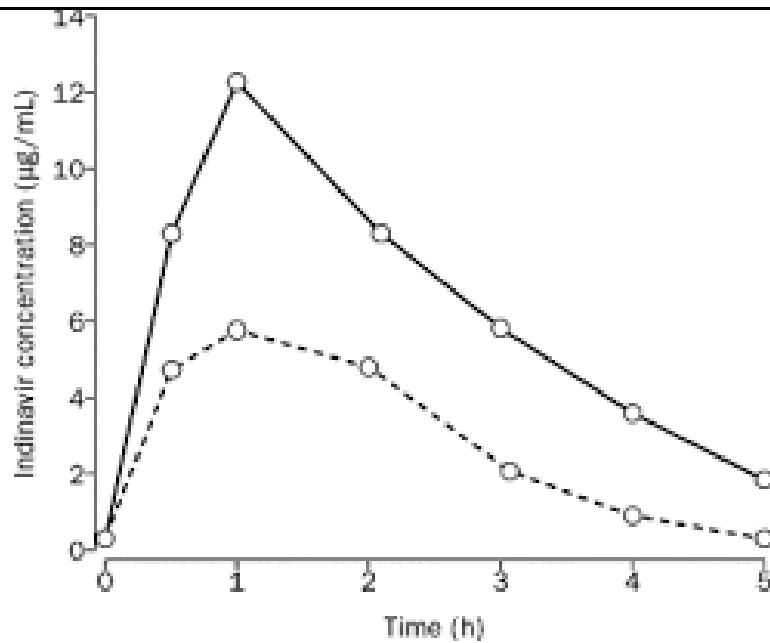
St. John's wort

- (Hypericum perforatum)
- Native to Europe.
- Tx depression (for many yrs) or topically for wounds.
- Still used in Germany.
- Blooms on the birthday of "John" the Baptist (24 June)
- Contains "hyperforin" in flowers & leaves
- A supplement (in teas, tablets, liquids & topical preps)
- Not approved by FDA



(* Wort = plant used for food or medicine)





Indinavir interaction with St John's wort

Application 1
(pharmacokinetic!)

St John's wort



Cyclosporine



↓ effect of cyclosporine

Application 2 (pharmacodynamic!)

St John's wort



TCA's



Serotonin syndrome

Other
common interactions

(1)

Co-trimoxazole



(methenamine)



- 1) ↑ Crystal-urea of co-trimoxazole
- 2) Mutual antagonism

(2)

Digoxin



Loop diuretics



↑ digoxin toxicity

(3)

Tetracyclines



Isotretenoin



↑ brain cancer!

(4)

Losartan



Hydro-choloro-thiazide



↓↓ BP + normalizing K

(5)

Hydrochlorothiazide



amiloride



↑ Diuresis + normalizing K

(6)

Penicillins



tetracyclines



↓↓ effect of penicillins

(7)

Vancomycin



gentamicin

 $\uparrow$ nephrotoxicity

(8)

Ampicillin



Sulbactam

 $\uparrow$ efficacy of Ampicillin



(9)

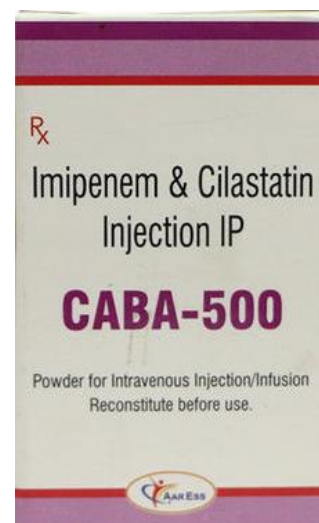
Imipenem



cilastatin



↓ nephrotoxicity of imipenem



(10)

Anticancer
(methotrexate)



folinic acid
(leucovorin)

= 5 formyl THFA



↓ bone marrow depression

(11)

Anticancer



Ondansetron



↓ vomiting caused by anticancers

(12)

Aspirin (antiplatelet)



Ibuprofen



- ↓ antiplatelet effect of Aspirin
(competition at COX)
- ↑ risk of peptic ulcer

(13)

Digoxin



Erythromycin or tetracycline



- ↓ intestinal normal flora
- ↑ toxicity of digoxin (2 fold; avoid)

Some digoxin is normally reduced by some intestinal flora into an inactive metabolite.

Can we memorize
all the interactions?

NO

Don't panic!



- 1- Only few interactions are serious
- 2- Some interactions are good!
- 3- Some drugs are safe (even at high doses; penicillins)
- 4- Some interactions occur on prolonged use only

So what do we do?



- 1- Memorize some common ones
- 2- Check (tables, databases in pocket refs, online or apps) with:
 - a. Strong CYP inducers or inhibitors
 - b. Drugs with narrow therapeutic index
 - c. Crucial drugs (e.g. contraceptives)
 - d. Long-term drugs
 - e. Certain patients (critically ill, hepatic or renal failure)
 - f. Multiple prescribers

- 3- If not known, use your assessment or consult esp if:
 - a- 2 drugs metabolized by 1 enzyme
 - b- 1 drug metabolized by an enzyme
& 1 drug is an inducer (↑) or an inhibitor (↓)

Drugs that need to be checked for interactions? (I Can Have Fun Heartily Out-Smarting Warring Drugs)

I = Immunosuppressant

C = Cancer drugs

H = HIV drugs

F = Fungal Drugs

H = Heart drugs

O = Oral contraceptives

S = Seizures

W = Warfarin

D = Diabetes Drugs

What is a common
factor?

- Prolonged use
- Serious toxicities

Databases

Medscape

NEWS & PERSPECTIVE

DRUGS & DISEASES

CME & EDUCATIO

Drug Interaction Checker

Enter a drug, OTC or herbal supplement:

 Print

1 Interaction Found

Patient Regimen

Clear All 

carbamazepine 

isoniazid 

Significant - Monitor Closely

isoniazid + carbamazepine

isoniazid will increase the level or effect of carbamazepine by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Use Caution/Monitor. Monitor plasma levels when used concomitantly

Drug Information Online
Drugs.com

Browse all medications [A](#) [B](#) [C](#) [D](#) [E](#) [F](#) [G](#) [H](#) [I](#) [J](#) [K](#) [L](#) [M](#) [N](#) [O](#) [P](#) [Q](#) [R](#) [S](#)

Enter a search term

Home → Interactions Checker

Drug Interactions Checker

Type in a drug name and select a result from the list. Repeat the process to add multiple drugs. When complete, save your list for future reference or check for interactions immediately.

Drug Name

Unsaved Drug List [Save](#) | [New list](#)

Aspirin Low Strength (aspirin) [x](#)

type in the names of the medications your taking here and click the add button and once down click on the Interactions button.

Lexicomp®

Enter drug, disease, or other keyword Limit Search to

[Interactions](#) [Drug I.D.](#) [Calculators](#) [I.V. Compatibility](#) [Patient Education](#) [Toxicology](#) [Fac](#)

Interactions

Selected Items

Drugs
None

Allergies
None

☒ Duplicate Drug Therapy

Search

Search Drugs
Enter drug name

Search Allergies
Enter allergy name

Important Product Information

Interactions DOES NOT address chemical compatibility re
Information regarding the compatibility of mixing two or more I
them together through the same I.V. administration line is avai
available to Institutional clients and others as an add-on from
hand section).

[Feedback](#) [Corporate](#) [User](#)

word Limit Search to Select Interface Language

ors I.V. Compatibility Patient Education Toxicology Facts & Comparisons® M

Search Interaction Analysis

3 2

Lexicomp Interaction Analysis

A = No known interaction
 C = Monitor therapy
 X = Avoid combination
B = No action needed
D = Consider therapy modification

View interaction detail by clicking on link.

D Aspirin (Salicylates) – Warfarin (Vitamin K Antagonists) *Depends on Dose*

Drug Interactions

Type the drug name (brand or generic) in the search field. Select the drug and click the (Add) button.

Enter search term:

Matching drug names: (500)

- A & D
- A & D Jr.
- A & D Ointment
- A Thru Zinc
- A To Z
- A+D
- A+D First Aid Ointment
- A-200 Pyrinaxone
- A-25
- A-3 Revised
- A-4 Revised
- A-42 Revised
- A-C-D Modified Bracco
- A-Carn-25

Drugs to check:

Capitalized item with asterisk (*) indicates allergy.

DRUGS METABOLIZED BY KNOWN P450'S Indiana University School of Medicine					
1A2	2B6	2C19	2C9	2D6	3A
Clozapine Cyclobenzaprine Duloxetine Fluvoxamine Haloperidol Ofazapine Tacrine Theophylline Tizanidine Triamterene Zileuton Zolmitriptan	Artemisinin Bupropion Cyclophosphamide Efavirenz Fosfamide Ketamine Meperidine Methadone Nevirapine Propofol Selegiline Sibutramine ThioTEPA	Carisoprodol Citalopram Clonidine Clomipramine Clobazam Cyclophosphamide Diazepam Esomeprazole Fluoxetine Imipramine Lamotrigine Nefinavir Omeprazole Phenytoin Pantoprazole Thalidomide Voriconazole	Angiotensin I receptor blocker Celecoxib Diclofenac Fluvastatin Flurbiprofen Ibuprofen Naproxen Oral Hypoglycemics Phenytoin Piroxicam Torsemide Valproic acid Warfarin Zafirlukast	Atomoxetine Carvedilol Clomipramine Codeine Desipramine Dextromethorphan Fluoxetine Metoprolol Ondansetron Oxycodone Propafenone Risperidone Tamoxifen Timolol Tramadol Venlafaxine	Alicantyl Alprazolam Buspirone Ca ⁺⁺ Channel Blockers Carbamazepine Cyclosporine Haloperidol HIV Protease Inhibitors (NOT pravastatin and rosuvastatin) Mefenamic Nevirapine PDG & inhibitors Tacrolimus Tamoxifen Triazolam Vincristine
Amiodarone Celecoxib Cimetidine Ciprofloxacin Fluvoxamine Levofloxacin	Clopidogrel ThioTEPA Ticlopidine Voriconazole	Cimetidine Felbamate Fluoxetine Fluvoxamine Isoniazid Ketoconazole Lamotrigine Omeprazole Oral Contraceptives Ticlopidine Voriconazole	Amiodarone Cimetidine Fluconazole Fluoxetine Metronidazole Paroxetine Voriconazole Zafirlukast	Amiodarone Cimetidine Buspirone Diphenhydramine Fluoxetine Haloperidol Paroxetine Quinidine Terbutaline	Amiodarone Cimetidine Buspirone Diltiazem & Verapamil Grapefruit Juice HIV Protease Inhibitors Itraconazole Ketoconazole Macrolide Antibiotics (NOT Azithromycin) Voriconazole
Carbamazepine Chlorzoxazone Rifampin Tobacco	Artemisinin Carbamazepine Efavirenz Nevirapine Phenytoin Rifampin Phenobarbital	Efavirenz Rifampin	Carbamazepine Nevirapine Phenobarbital Rifampin St. John's Wort	Carbamazepine Efavirenz & Nevirapine Phenytoin Phenobarbital Rifampin & Rifampin St. John's Wort	Carbamazepine Efavirenz & Nevirapine Phenytoin Phenobarbital Rifampin & Rifampin St. John's Wort
	Reduced in 10% of Caucasians	Absent in 15-30 % of Asians	Absent in ~ 1% of Caucasians	Absent in 7 % of Caucasians	

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Application 1

- Simvastatin + amiodarone (what do u think?)
- Can you use another statin?

Application 2

A patient is using tacrolimus after a kidney transplant. He is also using St. johns wort.

What would happen?

Managing Drug interactions

If serious:

- 1) Immediate cessation (if serious)
- 2) Deal with adverse effects
- 3) Change the drug (from same or another family)

If mild:

- 1) ↑ or ↓ dose
- 2) Monitor (and make adaptations)
- 3) Dose spacing (for interactions in GIT)
- 4) Proper supplement or food (K or high protein food)

Q) If u ↓ the dose of a drug because of a CYP inhibitor, and after that the patient stopped using the CYP inhibitor, what would u do?

E.g. fluconazol + simvastatin

What is new in the west?

Q) What do developed countries do to deal with drug interactions?

- 1) Programs to ↑ awareness (e.g. MedWatch)
- 2) New technologies

MEDWATCH

- FDA program launched in 1993 (in the USA)

- 4 goals:

- ↑ awareness of drugs
- Clarify what to report
- make it easy to report to the FDA
- provide feedback to health professionals



Some new technologies may
help prevent D-D interactions

- 1) Computerized prescription entry
- 2) Bar coding systems
- 3) Computerized medical records
- 4) Drug-interaction screening software

* But there are still some limitations!

So:

- 1) Do not rely completely on technologies.
- 2) Develop your own approach;
 - Be on the safe side
 - Develop your way of preventing drug interactions
- 3) Consult colleagues.

Final Notes

- 1) It is impossible to predict all interactions due to:
 - Genetic differences
 - Multiple CYP enzymes
 - Variable strength of inhibition or induction
 - Could be pharmacodynamics or pharmacokinetic
 - Could be by unknown mechanism
- 2) Interactions are often not bad:
 - Most interactions are good
 - Most drugs are safe even at high doses (penicillins)
 - CYP induction take 2-3 wks (inhibition is fast)

3) Note that ↑↑ metabolism of a drug may lead to:

- ↓ effect (usually)
- ↑ effect (for prodrugs)
- ↑ toxicity (e.g. isoniazid, paracetamol)

Finally!

1) To find me:

- YouTube Channel (Pharmacology for All)
- Facebook (Pharmacology by Dr Tareq Al-maqtari)
- Telegram channel (Pharma-Fun Pharmacology)
- Whatsapp groups

2) My 6 books (pharma-fun):

- مكتبة الموسلي أمام جامعة الناصر

😊 Thanks 😊

